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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,881	04/21/2005	Sergey Kipriyanov	4121-172	6340

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INTELLECTUAL PROPERTY / TECHNOLOGY LAW
PO BOX 14329
RESEARCH TRIANGLE PARK, NC 27709

EXAMINER	
NATARAJAN, MEERA	
ART UNIT	**PAPER NUMBER**
1643	
MAIL DATE	**DELIVERY MODE**
08/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,881	KIPRIYANOV ET AL.	
	Examiner	Art Unit	
	Meera Natarajan	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *4,5,18-21 and 24-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-17,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/10/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, Claims 1-17, 22, and 23 in the reply filed on 07/02/2007 is acknowledged. The traversal is on the ground(s) that the amended Claim 1, which now reads the combination of Claim 1 comprises at least two antibodies, **where both must be present**, are linked by a single inventive concept. The previous art applied, Kipriyanov et al. (Int J. Cancer 2001 – referenced in IDS 06/10/2005 on line AM) does not apply to amended Claim 1. However, Kudo et al. (Tohoku. J. Exp. Med. 1999, Vol. 188 p. 275-288) teach the simultaneous administration of two kinds of bispecific antibodies (anti-tumor X anti-CD3 plus anti-tumor X anti-CD28) together with lymphokine activated killer cells with a T cell phenotype inhibited growth of human xenotransplated tumors in SCID mice (see abstract). Therefore, Kudo et al. teach the technical feature recited in Claim 1 and the requirement is still deemed proper and is therefore made FINAL.

2. Applicant's election with traverse of the following species in the reply filed on 07/02/2007 is acknowledged.

Tumor antigen – CD19

T cell antigen – CD3

Effector cell antigen – CD16

Antibody – humanized antibody

Binding target - protein

The traversal is on the ground(s) that the species are related by a "commonality of operation, function and effect" and there would be no serious burden on the examiner to search all species. This is not found persuasive because as stated in the restriction requirement mailed 05/01/2007, the claims list several possible combinations of bispecific antibodies directed towards species of tumor antigens, t-cell antigens and effector cell antigens, all of which have distinct structures and functions. There are a large number of possible combinations, each requiring separate searches. Therefore, the requirement is still deemed proper and is made FINAL.

3. Claims 18-21 and 24-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 07/02/2007.

4. Claims 4 and 5 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 07/02/2007.

5. Claims 1-3, 6-17, 22 and 23 will be examined on the merits.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 13 recites wherein said antigen-binding domains "mimic" or correspond to V_H and V_L regions from a natural antibody. It is unclear what is meant by the term "mimic". Does this mean mimics the antibody's binding, mimics the antibody structure, mimics the antibody sequence? Clarification is required.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6, 9, 13, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Kudo et al. (Tohoku J. of Exp. Medicine Vol. 188, p275-288, 1999).

9. The Claims are drawn to a combination of at least two different multivalent antibodies, each one having at least two specificities, wherein one antibody is characterized by an antigen-binding domain specific to a tumor antigen and an antigen-binding domain specific to an antigen present on CD3-epsilon negative human effector cells and one antibody is characterized by an antigen-binding domain specific to a tumor antigen and an antigen-binding domain specific to an antigen present on human T-cells (species elected CD3).

10. Kudo et al. teach specific targeting immunotherapy of cancer with bispecific antibodies. Claim 1, 6, 9, and 13 are drawn to a composition comprising two bispecific antibodies, wherein one is directed to the T-cell antigen CD3 and a tumor antigen. Kudo et al. show that simultaneous administration of two kinds of bispecific antibodies (anti-tumor X anti-CD3 plus anti-tumor X anti-CD28) together with lymphokine activated killer cells with a T cell phenotype inhibited growth of human xenotransplanted tumors in SCID mice, while single bispecific antibody was without effect. Claim 16 is drawn to a composition according to Claim 1 and a third antibody having an antigen-binding domain different from the antigen-binding domains of the first and second antibody. Kudo et al. teach three kinds of bispecific antibodies (anti-tumor X anti-CD3, anti-tumor X anti-CD28, anti-tumor X anti-CD2) showed the highest cytotoxicity against tumor cells when given simultaneously with T cell phenotype cells or peripheral blood mononuclear cells *in vitro* and *in vivo* (see Abstract). The reference teaches each and every limitation of the claims.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 6-17, 22 and 23 rejected under 35 U.S.C. 103(a) as being unpatentable over Kudo et al. (Tohoku J. of Exp. Medicine Vol. 188, p275-288, 1999) in view of Kipriyanov et al. (International Journal of Molecular Medicine 2001; Vol. 8(1) p.S24) and Queen et al. (US Patent 6180370).

12. The claims are drawn to a combination of at least two different multivalent humanized antibodies, each one having at least two specificities, wherein one antibody is characterized by an antigen-binding domain specific to a tumor antigen (elected species CD19) and an antigen-binding domain specific to an antigen present on CD3-epsilon negative human effector cells (elected species CD16) and one antibody is characterized by an antigen-binding domain specific to a tumor antigen (elected species CD19) and an antigen-binding domain specific to an antigen present on human T-cells (elected species CD3).

13. The teachings of Kudo et al. have been presented in the 102(b) rejection set forth above. The reference does not teach the bispecific antibodies anti-CD19 X anti-CD3 and anti-CD19 X anti-CD16. The reference does not teach humanized antibodies linked to an effector molecule having a conformation suitable for biological activity or selective binding to a solid support or a pharmaceutical composition containing said antibodies. These deficiencies are made up for in Kipriyanov et al. (2001) and Queen et al.

14. Claims 2, 6, and 7 are drawn to bispecific antibodies directed towards CD19, CD3, and CD16 and Claim 22 is drawn to a composition of said antibodies. Kipriyanov et al. (2001) teach a panel of bispecific antibodies with the dual specificity to human CD19 or CD30 on non-Hodgkin's or Hodgkin's lymphoma cells, respectively, and either to CD3, CD28, or CD16 on human T cells or NK effector cells. It is widely known in the art that CD3 and CD28 are expressed on T cells, that CD16 is expressed on NK cells, i.e. CD3-epsilon negative cells, and that T cells and NK cells represent two different populations of effector cells. T cells and NK cells are the only effector cells mentioned in this document. A combination of bispecific antibodies retargeting different populations of human effector cells towards the tumor was reported to significantly enhance the therapeutic effect. Claim 17 is drawn to a composition comprising a first antibody which is specific to CD19 and CD16, a second antibody which is specific to CD19 and CD3, and a third antibody which is specific to CD28. Kipriyanov et al. teach the use of a tetravalent tandem diabody (Tandab) that is specific for both human CD19 and CD3. Treatment of SCID mice bearing an established Burkitt's lymphoma with human PBL,Tandab and anti-CD28 resulted in the complete elimination of tumors in all animals within ten days.

15. Claims 14 and 23 are drawn to a combination of humanized bispecific antibodies presented above and a composition containing a pharmaceutically acceptable carrier or a diagnostic composition. Queen et al. (Patent 6180370) teaches a method for preparing humanized immunoglobulins for novel therapeutic agents. Queen et al. also discloses pharmaceutical compositions comprising the humanized antibodies and

effector molecules such as chemical agents, proteins, or drugs linked to the antibody for diagnostic use (see columns 19 4th paragraph – column 20 2nd paragraph).

16. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the antibodies taught in Kipriyanov et al. for the antibodies taught in Kudo et al. and perform the same method of treatment. Kudo et al. even states "by conjugating antibodies (anti-CD3, anti-CD28, anti-CD16, anti-CD64, andti-CD89 or anti-CD2) to effector cells with antibodies to anti-tumor antigens, numerous bispecific antibodies can be produced. These various kinds of bispecific antibodies would cover most cancer tissues, and they might enable to start immunotherapy immediately after diagnosis" (see p. 285, 3rd paragraph). One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teaching in Kudo et al., Kipriyanov et al. and Queen et al. to humanize the bispecific antibodies taught in Kudo et al. and Kipriyanov et al. for immunotherapy treatment in humans.

Conclusion

17. Claims 1-3, 6, 7, 9-17, 22 and 23 are rejected.

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Meera Natarajan whose telephone number is 571-270-3058. The examiner can normally be reached on Monday-Thursday, 8:30AM-6:00PM, ALT. Friday. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MN

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER